REMARKS

Claims 1-35 are active.

Applicants thank the Examiner for entering the amendments in the reply filed January 4, 2008.

I. No *Prima Facie* Case of Obviousness for the Claimed Friability and Dissolution Profile

The Examiner has rejected claims 1-5, 7-27, and 29-31 over the combination of WO 01/43725 A1 to Gantt et al. in view of US 4,777,044 to Bins, and over the combination of Gantt in view of US 5,807,579 to Vilkov. Applicants respectfully traverse these rejections because the Examiner has not established a *prima facie* case of obviousness for the claimed friability and dissolution profile.

A. Friability

Applicants claimed tablets (provided by the claimed methods) have a friability of $\leq 0.3\%$. The claimed friability levels provide improved tablet strength and resistance to abrasion and attrition during transport and storage.[1]

1. The references in combination do not suggest a friability of $\leq 0.3\%$.

The combination of Gantt and Bins or Vilkov fails to properly support *prima facie* obviousness because those combination lack any disclosure of tablets having $\leq 0.3\%$ friability as in the present claims. Bins and Vilkov are silent on friability, and Gantt merely mentions that certain tablets have "low friability" without reporting values.[2] The Examiner provides no other evidence or knowledge in the art suggesting the claimed friability.

2. A rejection based on allegedly inherent disclosure of friability is improper.

Even if, *arguendo*, Gantt's, Bins', or Vilkov's tablets inherently disclosed the claimed friability values, the Examiner's rejection would still not be proper. An obviousness rejection cannot be predicated on a property inherent or unknown at the time of the invention, even if the inherency of a certain feature is later established. MPEP § 2141.02. Furthermore, to establish

[1] *See* page 12, para. [0030] of Applicants' specification.
[2] Page 5, lines 12-13.

inherency, the Examiner must provide technical reasoning or evidence that the property is necessarily present each and every time or necessarily flows from the teachings of the cited art (MPEP § 2112(IV)).

Here, the Examiner has provided no such evidence. The Examiner apparently suggests that one of ordinary skill in the art would optimize the compressed tablet of Gantt (modifying it to include Bins' or Vilkov's silicon dioxide) to arrive at the claimed friability. (Office Action at 5). But an inherency rejection is not proper if it is based on what would result due to optimization of conditions, rather than what is necessarily present in the prior art (MPEP § 2112(IV), citing *In re Rijckaert*, 28 USPQ2d 1955, 1957 (1993)). Accordingly, Applicants respectfully submit that the Examiner has not established *prima facie* obviousness based on inherent disclosure of ≤ 0.3% friability.

3. The Examiner improperly shifts the burden to Applicants to show that the prior art tablets do not have a friability of ≤ 0.3%.

The Examiner shifted the burden to Applicants to prove that the prior art tablets do not have the claimed friability. (Office Action at page 5). Applicants submit that such burden shifting is improper here because the Examiner concedes that none of Gantt, Bins, and Vilkov describe compositions identical in structure or composition to those claimed. MPEP § 2112.01(I) ("Where the claimed and prior art products are identical or substantially identical in structure or composition, . . . a *prima facie* case of either anticipation or obviousness has been established. When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." (citations omitted, emphasis added).) Indeed, the Office has repeatedly stated on the record that Gantt does not contain at least the claimed colloidal silicon dioxide, and Bins and Vilkov differ in a number of ways compared to the claimed tablets. Thus Applicants have no burden to prove that the tablets of the cited references do not meet the claimed ≤ 0.3% friability.

B. Dissolution profile

Applicants' claimed tablet provides a dissolution profile substantially corresponding to the following pattern (in purified water):

after 2 hours, about 30% to about 50% of the total potassium chloride is released;

after 4 hours, about 60% to about 75% of the total potassium chloride is released; and

after 8 hours, not less than 80% of the total potassium chloride is released.

Applicants note that this dissolution profile is indicative of the *in vivo* pharmacokinetic performance of the potassium chloride tablet. A tablet that meets this dissolution profile is a good candidate for clinical studies to establish bioequivalence to the reference extended release potassium chloride drug, K-Dur®. Thus this simple dissolution test can be a convenient proxy for a tablet's *in vivo* performance. (Indeed, in this case, Applicants developed a tablet exhibiting the dissolution profile of claim 1[3], and clinical studies confirmed that the tablet was bioequivalent to K-Dur®.)

1. The references in combination do not disclose the claimed dissolution profile.

Applicants respectfully submit that there is no suggestion in either reference that the disclosed tablets provide or would provide the claimed release profile. While Gantt makes a prophetic statement that its tablets "will" release "not more than 40% in one hour and not less than 80% over 8 hours," Gantt is silent as to release at the 2- and 4-hour time points, as in the present claims. Bins' tablets dissolve completely after only 6 to 7 minutes in conditions similar to those recited in the claims,[4] evidencing that Bins' tablets do not exhibit the claimed dissolution profile. Vilkov does not mention any release data at all. Therefore, no combination of Gantt, Bins, and/or Vilkov teach or suggest the claimed dissolution profile.

2. A rejection based on allegedly inherent disclosure of the dissolution profile is improper.

As discussed above, even if, *arguendo*, Gantt's, Bins', or Vilkov's tablets inherently disclosed the dissolution profile, an obviousness rejection cannot be predicated on a property inherent or unknown at the time of the invention. Furthermore, the Examiner has not established that the prior art tablets are identical in structure or composition such that the dissolution profile necessarily flows from their teachings (as required by MPEP 2112.01(I)). Accordingly,

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[3] See Example 10, pages 15-16, paragraphs [0039] and [0040] of the specification
[4] Col. 3, ll. 17-18. Bins' dissolution conditions are artificial intestinal juice at 7.5 pH, compared to purified water in the claims.

Applicants respectfully submit that the Examiner has not established *prima facie* obviousness based on inherent disclosure of the claimed dissolution profile.

II. Rebuttal of *Prima Facie* Case: The Examiner has not considered evidence of nonobviousness in the form of comparative results in the specification.

Even if the Examiner had established a *prima facie* case of obviousness, Applicants submit that it is rebutted by evidence of superior or unexpected results in the specification. MPEP § 2145. Applicants respectfully submit that the Examiner did not give any consideration of Applicants' comparative results from the specification, set forth in detail in the last response and briefly again here.

Objective evidence relevant to the issue of nonobviousness must be evaluated by the Examiner, including unexpected results. MPEP § 2141(II). Furthermore, examiners must consider comparative data in the specification intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims." MPEP § 716.01(a).

While the weight to be given any objective evidence is made on a case-by-case basis (MPEP § 2141(II)), the Examiner apparently gave no consideration whatsoever to Applicants' comparative data in the last office action. Indeed, the Examiner did not even acknowledge the two tables of data comparing the claimed compositions with compositions similar to Gantt (the primary reference relied upon by the Examiner and presumably the closest prior art of record).

Nonobviousness of Claims 1-35

As described in Applicants' last response, Table 1 presents data from the specification comparing tablets prepared with colloidal silicon dioxide (as presently claimed) and without (as in Gantt).

Table 1:
Comparison of Tablets/Compressible Blends With and Without Colloidal Silicon Dioxide

	Example 4*	Example 5*	Example 6*	Example 10
First coating polymer	ethylcellulose	ethylcellulose	ethylcellulose	ethylcellulose
Compressible coating: Plasticized Polymer	PVP + DBS	PVP + DBS	PVP + DBS	PVP + DBS
Additional ingredients in compressible blend	MCC	MCC	MCC	Colloidal SiO_2; MCC
Friability	1.5%	1.6%	0.9%	0.1%

* The tablets of Examples 4 and 5 are scored. The tablet of Example 6 is unscored.

The tablets containing colloidal silicon dioxide (Example 10) show a 9- to 16-fold improvement in friability over tablets lacking colloidal silicon dioxide (Examples 4-6). Thus Applicants submit that the comparative data in the specification showing the criticality of the colloidal silicon dioxide in the compression blend or tablet rebuts the Examiner's position that the processes or tablets of claims 1-35 are obvious.[5]

Nonobviousness of Claims 16, 27, and 33

Table 2 presents data from the specification comparing tablets containing colloidal silicon dioxide and substantially free of lubricants (as in claims 16, 27, and 33) with tablets lacking colloidal silicon dioxide and containing a significant amount of lubricant (as in Gantt).

Table 2:
Tablets with Colloidal Silicon Dioxide and Substantially Free of Lubricants
Compared to
Tablets without Colloidal Silicon Dioxide and Including a Lubricant

	Example 3	Example 11	Example 12*	Example 13*
Inner coating	ethylcellulose	ethylcellulose	ethylcellulose	ethylcellulose
Compressible coating: Plasticizer + Polymer	HPMC + PEG 400	ethylcellulose + diethylphthalate	ethylcellulose + diethylphthalate	ethylcellulose + diethylphthalate
Additional ingredients in compressible blend	MCC; Crospovidone; Mg stearate	Colloidal SiO_2; MCC; Crospovidone; Sodium lauryl sulfate	Colloidal SiO_2; MCC; Crospovidone	Colloidal SiO_2; MCC; Crospovidone
Hardness	1 kP	19.1 kP	22.4 kP	19.8 kP
Friability	Too friable to measure	0.17%	0.13%	0.25%

* Examples 12 and 13 contain the same ingredients but differ in their relative amounts.

The tablets containing colloidal silicon dioxide and substantially free of lubricants (Examples 11-13) show a ~20-fold improvement in hardness and far superior friability values compared to tablets containing the lubricant magnesium stearate and lacking colloidal silicon

[5] Although the comparative data in the specification is not identical to Gantt, Applicants submit the comparative examples in the specification are reasonably more closely related to the claimed tablets than those of Gantt (permissible under MPEP § 716.02(e)(I)).

dioxide (Example 3). Thus Applicants submit that the comparative data in the specification showing the criticality of the colloidal silicon dioxide and substantial lack of lubricant in the compression blend or tablet rebuts the Examiner's position that the processes or tablets of claims 16, 27, and 33 are obvious.[6]

The Examiner relies on *Ex parte Obiaya* for the proposition that "the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentablity when the differences would otherwise be obvious."[7] Applicants respectfully submit that *Ex parte Obiaya* is not applicable in this case where Applicants present comparative data measuring the same properties (hardness and friability) in the claimed tablets and the prior art. Compared to the "baseline" values in the prior art, Applicants' claimed tablets showed substantially improved values of the very same properties. This improvement shown by direct comparison is strong secondary evidence of nonobviousness. In contrast, the applicant in *Obiaya* pointed to a different property ("another advantage") that could not be compared directly to the prior art. Thus *Obiaya* is not relevant to the case at hand, where Applicants present data directly comparing the same parameter in the claimed and prior art tablets.

III. The Examiner has not properly interpreted the claim term "lubricant" and thus has not discredited Bins', Vilokov's, and Xilinas' teachings away from "substantially free of lubricants" (claims 16, 27, and 33).

Claims 16, 27, and 33 recite a compressible blend or tablet "substantially free of lubricants." (Applicants note that tablets including substantial amounts of lubricants such as magnesium stearate have extremely poor hardness and friability properties (see Examples 1-3), and those tablets substantially free of lubricant have substantially improved values (see Examples 10-13)).

During prosecution, the pending claims must be given their broadest reasonable interpretation consistent with the specification. MPEP §2111. Furthermore, an applicant may act

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[6] Applicants point out that the tablet/compression blend of Example 3 contains the same ingredients as Examples 1 and 2 of Gantt, the primary reference cited by the Examiner (presumably what the Examiner apparently considers to be the closest prior art of record). Thus the comparison provided by the examples in the present specification are effectively a direct comparison to Gantt.

[7] Office Action at page 8.

as his own lexicographer to define a claim term (explicitly or implicitly) in the specification, and that meaning trumps other possible meanings used in the art. MPEP § 2111.01(IV). Here, Applicants' specification clearly defines "lubricant" to encompass magnesium stearate[8] and "substantially lubricant-free" to exclude magnesium stearate in amounts typically used for lubrication.[9] Thus claims 16, 27, and 33, which recite "substantially free of lubricant" cannot encompass substantial amounts of magnesium stearate.

The Examiner apparently argues that claims 16, 27, and 33 must include magnesium stearate because Xilinas (US 2008/02076673) identifies magnesium stearate as a surfactant. (Office Action at 9). Applicants note that claims 16 and 27 do not recite the term "surfactant," and thus Xilinas' teaching is simply irrelevant to those claims. While claim 33 does recite a surfactant, this claim excludes substantial amounts of magnesium stearate under the only reasonable interpretation of "substantially free of lubricants," as discussed above. The Examiner apparently argues that the tablet of claim 33 can include magnesium stearate because Xilinas calls it by a different name (surfactant). However, Applicants respectfully submit that this interpretation is unreasonable and inconsistent with Applicants' definition of "substantially lubricant free" in the specification (impermissible under MPEP § 2111.01(III)).

Bins, Vilkov, and Xilinas teach away from tablets "substantially free of lubricants."

Under the only reasonable interpretation of the term "substantially free of lubricants" permitted by Applicants' specification, claims 16, 27, and 33 cannot encompass magnesium stearate. The art cited by the Examiner, in combination, reasonably teach the skilled artisan to include magnesium stearate and thus teach away from "substantially free of lubricants." Bins's preferred teaching and sole example teach away from this limitation because they include "a lubricating agent e.g. magnesium stearate." Likewise, Vilkov's preferred and "especially preferred" tablet mixtures and the sole example all teach incorporation of magnesium stearate.[10] Furthermore, Xilinas' preferred teachings and all examples of compositions include magnesium

[8] Page 10, paragraphs [0024] and [0026].
[9] Page 10, paragraph [0024] and page 11, paragraph [0028].
[10] Col. 3, ll. 13-21; col 3, ll. 60-65.

stearate.[11] Gantt does not teach a clear preference and provides examples with and without magnesium stearate.[12] Faced with the combination of these references, one skilled in the art would reasonably follow the strong teachings Bins, Vilkov, and Xilinas to include magnesium stearate, which would provide a tablet not "substantially free of lubricants."

The Examiner has not provided any evidence to discredit Bins', Vilkov's, and Xilinas' strong teachings away from "substantially free of lubricants." Accordingly, Applicants respectfully submit that the Examiner cannot reasonably maintain the rejection of claims 16, 27, and 33 as obvious in light of the clear teachings away in the cited art.

For the reasons stated above, Applicants respectfully request that the rejection be withdrawn, and submit that the present application is now in condition for allowance.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

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[11] Paragraph [0115] and Examples 1 and 7.
[12] Example 3 of Gantt uses magnesium stearate.